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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,181	09/09/2005	Judith A. Varner	UCSD-08879	5608

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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06/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,181	VARNER ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 3/20/08 was entered.

Applicant elected previously the following species: (a) endothelial cell as a species of a cell; and (b) cancer as a species of a pathological condition.

Amended claims 25-40 are pending in the present application, and they are examined on the merits herein with the aforementioned elected species.

Information Disclosure Statement

The information disclosure statement filed 3/20/08 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (J. Biol. Chem. 275:33920-33928, 2000: IDS) in view of Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997), Srivastava et al. (Mol. Cell. Biol. 18:3509-3517, 1998) and Mixson, A. J. (US 6,080,728) for the same reasons already set forth in the Office action mailed on 11/21/07 (pages 2-5). ***The same rejection is restated below.***

Kim et al already taught that agents that activate intracellular protein kinase A (PKA), such as forskolin, dibutyryl cAMP or $\alpha 5\beta 1$ antagonists, suppress endothelial cell migration on vitronectin *in vitro* or angiogenesis *in vivo*, while inhibitors of PKA reverse the anti-migratory or anti-angiogenic effects (see at least the abstract; page 33924, col. 2, last paragraph continues to first paragraph of col. 1 on page 33925; Figures 4-7). Kim et al further stated "These studies also suggest the potential use of PKA agonists in

the treatment of angiogenic diseases, including cancer and arthritis" (page 33927, col. 2, last paragraph continues to first two lines in col. 1 of page 33928).

Kim et al did not teach specifically the use of an isolated nucleotide sequence encoding a protein comprising a protein kinase A (PKA) catalytic subunit as the agent or the PKA agonist in a method for reducing angiogenesis or for increasing apoptosis in a tissue comprising endothelial cells (elected species), and/or wherein the tissue is in a subject having cancer (elected species) as a pathological condition associated with angiogenesis.

However, at the effective filing date of the present application (6/25/02) Kim et al (Biochem. Biophys. Res. Comm. 232:469-473, 1997) already taught that overexpression of a protein kinase A catalytic subunit meditated by a recombinant retroviral vector in SK-N-SH human neuroblastoma cells resulted in a 3-fold increased PKA activity in the absence of cAMP, increased type II protein kinase A activity and cellular growth inhibition (see at least the abstract; and Results and Discussion on pages 470-472).

Additionally, Srivastava et al taught that activation of cAMP-dependent protein kinase A by Paclitaxel, forskolin or okadaic acid induced Bcl2 hyperphosphorylation and apoptosis in cancer cells which were blocked by the PKA inhibitor Rp diastereomers of cAMP (see at least the abstract; page 3511, col. 2, the section entitled "cAMP-dependent protein kinase is involved in Bcl2 phosphorylation", page 3510, col. 2, the section entitled "Nuclear morphology").

Furthermore, at the effective filing date of the present application Mixson also taught successfully at least a method for inhibting tumor growth in a subject bearing a tumor comprising injection of DNA encoding at least one anti-angiogenic protein or peptide specifically targeting the tumor and/or tumor vasculature (see at least Summary of the Invention; and issued claims). Mixson disclosed that the method is applicable to different types of tumors, including primary tumors and their metastases or malignant tumor cells, and all of the tumors are very dependent on blood supply to sustain their growth (col. 10, lines 15-19; col. 4, lines 47-54 and example 1).

Accordingly, it would have been obvious for an ordinary skilled artisan at the time of invention was made to modify the teachings of Kim et al (J. Biol. Chem. 275:33920-33928, 2000) by also expressing a nucleotide sequence encoding a protein comprising a protein kinase A catalytic subunit in a tissue comprising endothelial cells, for example in a tumor vasculature, to induce anti-angiogenic effects and/or apoptotic effects to inhibit tumor growth in light of the teachings of Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997), Srivastava et al., and Mixson, A. J.

An ordinary skilled artisan would have been motivated to carry out the above modification because expression a nucleotide encoding a protein kinase A catalytic subunit has been shown to be a means for the activation of intracellular protein kinase A that has been demonstrated to be involved in the suppression of endothelial cell migration on vitronectin *in vitro*, inhibiting angiogenesis *in vivo*, inhibiting human neuroblastoma cell growth *in vitro*, as well as the induction of Bcl2 hyperphosphorylation and apoptosis in cancer cells *in vitro*.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Kim et al (J. Biol. Chem. 275:33920-33928, 2000), Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997), Srivastava et al. and Mixson, A. J.; coupled with a high level of skill of an ordinary artisan in the relevant art.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 3/20/08 (pages 5-6) along with the Declaration under 37 C.F.R. 1.132 by Dr. Judith Varner filed on 3/20/08 have been fully considered but they are respectfully not found persuasive for overcoming the rejection of record for the following reasons.

It is noted that Applicant' arguments (pages 5-6) rely exclusively on the Declaration of Dr. Judith Varner.

The Declaration under 37 CFR 1.132 filed 3/20/08 is insufficient to overcome the rejection of claims 25-40 based upon Kim et al. (J. Biol. Chem. 275:33920-33928, 2000: IDS) in view of Kim et al. (Biochem. Biophys. Res. Comm. 232:469-473, 1997), Srivastava et al. (Mol. Cell. Biol. 18:3509-3517, 1998) and Mixson, A. J. (US 6,080,728) under 35 U.S.C. 103(a) because:

1. With respect to the primary reference of Kim et al (2000), Applicants argued that it was not clear whether the anti-angiogenic effects of forskolin and cAMP were the result of activation of Epac or protein kinase A because forskolin's and cAMP's

effect on angiogenesis could have been mediated by any number of pathways, including via Epac and independently of protein kinase A. Additionally, with respect to claims 33-40, the reference is silent on apoptosis and that cell migration and angiogenesis are different phenomena from apoptosis.

It is noted that **the conclusions of the study of Kim et al were also based on results obtained from protein kinase inhibitor studies, including the use of H89 which is a specific and selective inhibitor of protein kinase A** (see the abstract and at least sections entitled "Regulation of Integrin cross-talk by protein kinase A" and "Integrin alpa5beta1 and protein kinase A regulation of alphavbeta3-mediated angiogensis in vivo"). Kim et al taught specifically that **inhibitors of PKA reverse the anti-migratory or anti-angiogenic effects** (see at least the abstract; page 33924, col. 2, last paragraph continues to first paragraph of col. 1 on page 33925; Figures 4-7). Kim et al further stated "These studies also suggest **the potential use of PKA agonists in the treatment of angiogenic diseases, including cancer and arthritis**" (page 33927, col. 2, last paragraph continues to first two lines in col. 1 of page 33928). Therefore, an ordinary skilled artisan would conclude clearly **that the suppression of angiogenesis *in vivo* is mediated by PKA, and not by other protein kinases or by other pathways suggested by Applicants**.

With respect to claims 33-40, please note that the above rejection is applied under 35 U.S.C. 103(a) and therefore the Kim et al (2000) reference does not have to disclose every limitation of the claims. Other cited references supplement the teachings

of Kim et al (2000) for the reasons set forth above as well as explanation elaborated below.

2. With respect to the Kim et al. (1997) reference, Applicants argued that the reference only discloses the role of protein kinase A on cell growth of neuroblastoma cells relating to different cell type (neuroblastoma vs endothelial cells) and different phenomenon (growth vs angiogenesis or growth vs apoptosis). With respect to the Mixson reference, Applicants argued that the reference does not disclose that tumor growth inhibition results in reducing angiogenesis, and that the reference relates to different phenomenon (tumor growth) from the recited phenomenon which is angiogenesis or apoptosis. Finally, with respect to the Srivastava et al reference, Applicants argued that the reference refers to apoptosis which is a different phenomenon from the recited angiogenesis.

Firstly, the examiner notes that Applicants consider each cited references in total isolation one from the others; and this is improper.

Secondly, as already stated above that the primary Kim et al (2000) reference clearly disclosed that **the suppression of angiogenesis *in vivo* is mediated by PKA and suggested explicitly the potential use of PKA agonists in the treatment of angiogenic diseases, including cancer and arthritis** (page 33927, col. 2, last paragraph continues to first two lines in col. 1 of page 33928).

Thirdly, Mixson taught successfully and clearly a method for inhibting tumor growth in a subject bearing a tumor comprising injection of DNA encoding at least one anti-angiogenic protein or peptide specifically targeting **the tumor and/or tumor**

vasculature (made up of endothelial cells); and all of the tumors are very dependent on blood supply (requiring angiogenesis) to sustain their growth (col. 10, lines 15-19; col. 4, lines 47-54 and example 1). Moreover, Srivastava et al also taught that activation of cAMP-dependent protein kinase A by Paclitaxel, forskolin or okadaic acid induced Bcl2 hyperphosphorylation and **apoptosis in cancer cells which were blocked by the PKA inhibitor Rp diastereomers of cAMP**. Furthermore, Kim et al (1997) already taught that **overexpression of a protein kinase A catalytic subunit meditated by a recombinant retroviral vector in SK-N-SH human neuroblastoma cells resulted in a 3-fold increased PKA activity in the absence of cAMP, increased type II protein kinase A activity and cellular growth inhibition.** Therefore, all of the cited references are all related a method of suppressing tumor growth in a subject via the killing of tumor cells directly (apoptosis) and/or indirectly via the suppression of tumor vascular endothelial cell growth (angiogenesis) using PKA agonists, including an expression vector encoding a protein comprising a protein kinase A (PKA) catalytic subunit.

Fourthly, there is no factual evidence provided by Applicants indicated or suggested that **the PKA inhibitor Rp diastereomers of cAMP used by Srivastava et al is non-specific and that it can act on pathways other than via protein kinase A. Moreover, Srivastava et al clearly concluded that protein kinase A is involved in the induction of Bcl2 hyperphosphorylation and induction of apoptosis in a peer-reviewed article (see at least the abstract).**

Accordingly, claims 25-40 are still rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (2000) in view of Kim et al. (1997), Srivastava et al. and Mixson, A. J. for the reasons set forth above.

Conclusions

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN, Ph.D./

Primary Examiner, Art Unit 1633